Vaccine Safety:
Following Vaccines from Pre-licensure to Post-licensure

Barbara Wolicki RN, BSN
Michigan Department of Community Health
Division of Immunization
WolickiB@michigan.gov

Overview

- Monitoring and assuring vaccine safety from all perspectives:
  - Vaccine Manufacturers
  - FDA (Food and Drug Administration)
  - CDC (Centers for Disease Control)
  - Healthcare Providers: Public and Private
  - Parents/Families/Clients

Vaccine Testing

- A vaccine is first tested in a laboratory then in animals
- The vaccine then goes through 3 test phases:
  - Phase I: Immune Response Studies
  - Phase II: Dosage Studies
  - Phase III: Large Studies
- FDA monitors data from each phase for vaccine safety and subsequently, vaccine efficacy

Phase I: Immune Response Studies

- A small number of volunteers receive the vaccine (about 10-100 people)
- Focus:
  - To understand how a person's immune system will respond to the vaccine

Phase II: Dosage Studies

- Phase II timeframe varies from months to years
- Involves hundreds of volunteers
- People receive different amounts of the vaccine to determine:
  - The most effective use of the vaccine
  - The best dose for effectiveness and safety
  - The right number of doses
- Any/all side effects are recorded
  - Local reactions
  - General body reactions

Phase III: Large Studies

- Phase III timeframe may be several years
- Usually involves thousands of volunteers
  - Some may receive another licensed vaccine instead of the vaccine under study
- Continued monitoring of adverse effects
  - From sore arm to a serious reaction
- Focus:
  - To determine how effective the vaccine will be in protecting a person from disease

FDA Approval of a Vaccine

- All data from these studies is submitted to the FDA for review and approval
- The FDA must approve:
  - The package insert
  - Manufacturing plans
    - includes inspection of plants
- After approval, vaccine is licensed for use in the U.S.

Tracking Vaccines After Licensing "Phase IV"

- Continual tracking of thousands of people who were immunized with the vaccine in clinical trials
  - Gives valuable information about the vaccine's long-term safety and effectiveness
- FDA requires the drug company to test samples of each vaccine lot for safety, potency and purity
- FDA conducts on-going inspections of the manufacturing facilities

Advisory Committee on Immunization Practices (ACIP)

- Forms workgroups to study new vaccines
- Makes initial & on-going recommendations for the use of each vaccine
  - Gives guidance on practical use of vaccine
  - Recommendations published in Morbidity and Mortality Weekly Reader (MMWR)
  - Found at http://cdc.gov/vaccines/recs

Effects of Vaccine Safety Monitoring

- Pre-licensure
  - Clinical trails are closely monitored during each phase by the FDA
- Post-licensure
  - Rare side effects and delayed reactions may not happen until the vaccine is given to millions of people
  - Mechanisms to monitor these events are needed

What is VAERS?

- Vaccine Adverse Event Reporting System
- National passive reporting system that accepts reports from the public on adverse events associated with vaccines licensed in the U.S.
  - Approximately 30,000 reports per year
  - 10-15% classified as serious
    - Causing disability, hospitalization, life-threatening illness or death
- Anyone can report to VAERS—
  medical personnel, parents, self

Why use VAERS?

- VAERS data are monitored to:
  - Detect new, unusual or rare vaccine adverse events
  - Monitor increases in known adverse events
  - Identify potential patient risk factors for particular types of adverse events
  - Identify vaccine lots with increased numbers or types of reported adverse events
  - Assess the safety of newly licensed vaccines

VAERS

- VAERS website: http://vaers.hhs.gov
- Information line: (800) 822-7967
- Email inquires: info@vaers.org
- Fax inquires: (877) 721-0366

Pre-addressed postage paid report forms are available by calling VAERS information line

Vaccine Safety Datalink (VSD) Project

- Developed by CDC in 1990
- Stores comprehensive medical records & immunization histories for 5.5 mil people annually
  - Members of participating managed care organizations
- Monitors for possible side effects of vaccination
- At present, examining *potential* associations between vaccines and serious side effects
  - Hep B vaccine and hair loss
  - Flu vaccine and Bell's Palsy

Institute for Safe Medication Practice (ISMP)

- Developed a confidential national voluntary *Medication Errors Reporting Program* (MERP)
- Health care professionals and consumers are encouraged to submit reports
- Gathers information* and forwards it to the FDA, the manufacturers and others to inform them:
  - About pharmaceutical labeling, packaging and nomenclature issues that may foster errors

*Your name and contact information are withheld unless you grant permission to include

Further ISMP Information

- On-line reporting form will ask you to include any of the following incidences:
  - The actual medication error
  - The potential error you are concerned about
  - A error that almost occurred
- It is recommended that all vaccine medical errors *without* adverse event be reported using this program
- ISMP website:
  - http://www.ismp.org/reporterrors.asp

Adverse Event: Coincidental or Caused by the Vaccine?

	Adverse Event	No Adverse Event
Vaccine	A	B
No vaccine	C	D

- Is there an increased risk of the adverse event in the vaccinated group verses the unvaccinated group?

Do These Monitoring Systems Make a Difference?

- Syncope after vaccination
- Vaccine product containers
- Oral Polio Vaccine (OPV) verses Inactivated Polio Vaccine (IPV)
- RotaSheild® (Rota, RV) vaccine
- Inadvertent Misadministration of MCV4

Oral Polio vs Inactivated Polio Vaccines

- Paralytic polio cases peaked in 1952 with more than 21,000 reported
- In 1955, IPV and in 1961, OPV were approved for use in the U.S.
- Last case of wild-virus polio in U.S in 1979 with eradication in Western Hemisphere in 1991
- From 1980-1999, 152 polio cases reported in U.S
  - 6 cases imported; 2 cases not determined
  - 144 cases Vaccine Associated Paralytic Polio (VAPP) after vaccination with OPV
- In 2000, U.S recommendation changed to all IPV schedule; last VAPP case in 1999

RotaSheild ® Rotavirus Vaccine

- In 1998, RotaSheild® (Wyeth-Lederle) was approved by FDA and recommended by CDC for routine use
- Recommendation withdrawn within 1 year and Wyeth voluntarily withdrew vaccine from market
- Associated with increased risk for intussusception
  - 20-fold increase within 3-14 days of 1st dose
  - 5-fold increase within 3-14 days of 2nd dose

RotaTeq® (RV5) and Rotarix® (RV1) Vaccines

- RotaTeq® (Merck)
  - Phase III studies included 70,000 infants 6-12 wks of age
  - Approved in 2/06; post-licensure studies 2/06-2/07 showed no increase risk of intussuseption
- Rotarix® (GSK)
  - Controlled safety study included 63,225 infants followed for 31 days post-vaccination and a subset of 20,164 infants followed for 1 year; concluded without evidence of increase risk for intussuseption
  - Approved in 4/08; post-licensure studies on-going

Inadvertent Misadministration of MCV4 (Menactra®; sanofi pasture)

- Meningococcal conjugate vaccine (MCV4) licensed in 2005 to be given IM
- Meningococcal polysaccharide vaccine (MPSV4) licensed in 1978 to be given SC
- From June-August 2005, reports of 101 persons receiving MCV4 via SC route
- 38 MCV4 SC vaccinees agreed to participate in serologic testing to determine immune response
- Outcome:
  - Titers showed adequate response to MCV4 vaccine in nearly all SC vaccinees
  - Revaccination was not recommended

YOUR Role In Promoting Vaccine Safety

JoEllen Wolicki BSN RN
Division of Immunization
Michigan Department of Community Health
248-330-9989 wolickij@michigan.gov

Overview

- We have outlined what pharmaceutical companies and government agencies do to assure vaccines are safe and effective
- Next, lets examine the role of medical staff in assuring vaccine safety

Vaccine Safety

- Immunization providers can help to ensure the safety and efficacy of vaccines through:
  - Proper storage and handling
  - Correct vaccine administration
  - Complete documentation
- These are included in the Standards for Childhood and Adult Immunization Practices

Vaccine Management Concerns

- Increasing number of vaccines and presentations shrinking available storage space
- Nationally, exposure of inactivated vaccines to freezing temperatures is the most common storage error
- In Michigan, total vaccine losses the Vaccines for Children program for FY 07:
  - 797 losses = 34,518 doses = $647,611.13
  - Expired vaccines is the most frequent reason for vaccine loss

Equipment Basics

- Standard household refrigerator/freezer manufactured in the last 10 years
- Refrigerators should have
  - separate, sealed refrigerator and freezer compartments with external doors
  - separate temperature controls for refrigerator and freezer compartments
  - enough room to store the year's largest inventory without crowding

Equipment Basics

- Small single-door units (dormitory-style) may be used for temporarily storing **small quantities** of refrigerated vaccines **if** the refrigerator compartment can maintain temperatures at between 35° to 46°F
- Small single-door combined refrigerator-freezer units should NOT be used for:
  - Permanent storage for any vaccines
  - Vaccines that must be kept frozen

Vaccine Management

- All personnel should be familiar with standard procedures for vaccine management
- Vaccine management includes a written plan for:
  1. Storage and handling
     a. Ordering vaccine
     b. Accepting a vaccine delivery
     c. Inventory control-preventing expired vaccine, storing at appropriate temperature, etc
  2. Emergency planning
     a. Including procedures for vaccine relocation in the event of a power failure or mechanical difficulty
  3. Taking action when vaccines are compromised
- Sample forms for vaccine management are available at www.aimtoolkit.org

Ordering & Accepting Vaccine Delivery

- Guidelines should include information on:
  - Ordering and stocking enough vaccine to ensure that there is an adequate supply to meet the needs of the patients
  - Arranging for vaccine deliveries to be made only when the clinic is open
  - Staff who accept vaccine deliveries must be aware of the importance of maintaining the cold chain and of the need to **immediately** store the vaccine shipment appropriately

Storing Vaccines

- Designate one person as the vaccine coordinator
  - Assign a back-up person
- Storage procedures should include:
  - Storing vaccines at recommended temperatures at all times
  - Placing vaccine in the middle of the compartment, away from the coils, walls, floor, and cold air vent
  - Vaccines should not be stored in the doors
  - Store all opened and unopened vials of vaccine in their boxes so that their contents and expiration dates are easily identifiable
- Post details of proper storage and handling on or near the refrigerator

Inventory Management

- Place a certified calibrated thermometer in both the refrigerator and freezer
- Thermometers (and any other monitoring equipment) should be:
  - Designed for refrigerators or freezers
  - Certified
  - In good working order
- Written storage procedures should include:
  - Maintaining complete and accurate stock records
  - Monitoring the temperature of all units that store vaccine twice a day- maintain a log book
  - Placing water bottles in the refrigerator and ice packs in the freezer to help maintain a constant temperature
  - Storing diluents
    - Diluents packaged separately from their vaccines may be stored at room temperature or in the refrigerator
    - Store diluents packaged with their vaccines in the refrigerator

Emergency Plan

- Written protocols for compromised vaccines are critical
- Take action when vaccine is compromised
  - Vaccine can be compromised by power outages or by being left out on the counter
  - Do not allow vaccine to remain in a nonfunctioning unit
- Separate the compromised vaccines and store appropriately
- Follow your Emergency Response Plan
  - Call the vaccine manufacturers for further instructions
  - DO NOT automatically throw away vaccines
- Document what you did and the outcome
- Sample emergency response worksheet at www.aimtoolkit.org

Vaccine Administration Challenges

- 2002 study:
  - 10% of immunizations given are erroneous
  - 50% of vaccine errors associated with immunizations occurred in administration
  - Out of 16,211 children only 9% received immunizations at recommended ages
- Reasons for errors:
  - Failure to follow protocols
  - Similar packaging for different vaccines
  - Knowledge deficits
  - Administration errors increase with newer vaccines

Vaccine Administration Knowledge

- Overall didn't think vaccines were medications
- 70% didn't know the five rights of medication administration
- 78% didn't feel needle size was important
- Only 55% felt that the correct route was very important
- 90% didn't realize an error occurred until after it happened
- 38% didn't report errors because they didn't know they made an error

Looking Closely To Prevent Errors

- Ensure that the right vaccine is given to the right patient
- Many vaccines with similar letters are licensed for different ages. Example:
  - DTaP 6 weeks thru 6 years of age
  - Td 7 years of age and older
  - Tdap
    - Boostrix® 10 thru 18 years of age
    - Adacel® 11 thru 64 years of age
- Employ measures to help differentiate vaccines
  - Color code with stickers
  - Label the boxes for the ages that it is licensed for
  - Store infant, adolescent and adult vaccines on different shelves in the storage unit

Preparing Vaccines Safely

- Do not pre-fill syringes
  - Only give shots/vaccines that you have drawn up
- Protect vaccines from light!
  - How well the vaccines work can be affected
- Reconstitute vaccines only with the diluent supplied by the manufacturer
  - Make sure the diluent (and vaccine) are not expired
  - Expired vaccine and/or diluent should never be administered
- Never mix vaccines in the same syringe unless they are specifically approved for mixing by the FDA
- Post vaccine preparation guidelines for easy reference

Injection Process

- Standing orders can help to standardize immunization practices between clinic staff
- Always administer vaccines by the right route and site
  - Administered vaccines in the deltoid or anterolateral aspect of the thigh only
- IM needle lengths should be long enough to reach the deep into the muscle mass to prevent the vaccine from seeping into subcutaneous tissue
  - Professional judgment is appropriate when choosing needle length
- A recent study found the longer needles - 1 inch - were associated with fewer local reactions for vaccines given at 2, 4 and 6 months of age

Injections and Adolescents

- Syncope has been reported after vaccination in adolescents
- 62% of the syncope reports VAERS received during January 1, 2005 – July 31, 2007 were among children aged 11 to 18 years
- ACIP suggests that vaccine recipients sit or lie down for 15 minutes after immunization

Adverse Reactions

- No vaccine is completely safe and effective in every person
- Screening is key to preventing serious adverse reactions
- Screen for both permanent and temporary contraindications at ***every*** vaccination visit
- Vaccine Information Statements (VIS) outline adverse reactions
  - Give a VIS ***prior*** to administering the vaccine
  - Give a VIS with ***each dose*** of vaccine
- Screening questionnaires for adults and children are available www.aimtoolkit.org

Managing Vaccine Reactions

- Most people experience no side effects, or only mild ones, following immunization
- Any provider who administers vaccines should have procedures for the emergency care of a person who experiences an anaphylactic reaction
- Epinephrine and equipment for maintaining an airway should be available for immediate use
- All vaccine providers should be familiar with the office emergency plan, and should be certified in cardiopulmonary resuscitation
- Examples of protocols for medical management of vaccines reactions for children and adults – www.aimtoolkit.org

Vaccine Administration Errors

- Don't guess – seek more information
  - Not all vaccines given incorrectly need to be repeated
  - Resources to call include local or state health departments
- If the dose of vaccine should be repeated consider the live-live rule or any minimum intervals that may apply
- Remember to report vaccine medication errors to Institute for Safe Medical Practices

Documentation & Vaccine Safety

- Complete and correct documentation for all vaccines is critical
- VAERS reports ask for specific information regarding vaccines administered within 4 weeks of the adverse event including:
  - Vaccine type
  - Route
  - Site
  - Manufacturer
  - Lot number
  - Number of previous doses
  - Date of administration

Vaccine Safety & You

- Incorporate measures to ensure the immunization practices in YOUR clinic are based on proper storage, handling and administration guidelines
- Communicate all immunization policies, protocols and/or standing orders to all staff
  - Include in both vaccine management and administration in orientation for new staff

Vaccine Management & Administration Resources

- 2008 AIM Tool Kit aimtoolkit.org
- MDCH michigan.gov/immunize
- CDC cdc.gov/vaccines
- IAC immunize.org
- AAP Red Book aap.org

Talking with Families about Vaccine

Patricia Vranesich RN BSN
Outreach, Education and Surveillance
Division of Immunization
Michigan Department of Community Health

Overview

- We have discussed:
  - What steps are taken to assure vaccine is safe
  - What we call can do to promote vaccine safety
- In the next few minutes:
  - What concerns families have
  - How we can talk with families about vaccine

Challenges

- Low disease awareness = increased focus on vaccine risks
- From fear of disease to fear of adverse events
- 1 out of 20 parents sought medical attention for a child due to an adverse event following immunization

Parental concerns and medical-seeking behavior after immunization. Am J Prev Med. 2006;31:32-5.

Challenges

- Childhood immunization schedule is growing in length and complexity
- Vaccinations are mandated
- Temporal associations are powerful
  - **Post hoc ergo propter hoc**, "after this, therefore because of this"

Parent Concerns

- Parents have concerns:
  - vaccines may cause learning disabilities **17%**
  - children get too many vaccines **21%**
  - vaccines are not tested enough for safety **21%**
  - the ingredients in vaccines are unsafe **24%**
  - it is painful for children to get so many shots during one doctor's visit **31%**

Healthstyles Survey, 2003

Parents' Concerns

- No causal evidence
  - SIDS, Autism, Multiple Sclerosis
- Research
  - Pharmaceutical bias
- Conflict of Interest
  - Government mandates, drug lobbyists

Parents' Concerns

- Uncertainty
  - Some MDs question the value
  - Conflicting assertions
- Mistrust
- Perceptions of arrogance
- Patient Advocacy
  - Standing up for the little guy

Consequences

- 15% of under-immunization was attributable to parental attitudes, beliefs, and behaviors[1]
- The estimated number of unvaccinated children aged 19-35 months increased from 14,700 in 1995 to 24,000 in 2000[2]
- 48% of parents of unvaccinated children expressed concerns about vaccine safety[2]

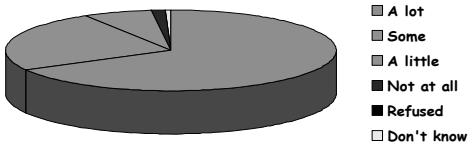
[1]Underimmunization Among Children: Effects of Vaccine Safety Concerns on Immunization Status. Pediatrics 2004 p 16-22

[2]Parents attitudinal and social influences on childhood vaccination. Health Education Research 2004 p 341-348

Who should talk (with families)

- Many people have questions & concerns, and are looking for reassuring answers
- Health care professionals
  - Have the credibility to provide those answers
  - Are considered reliable and authoritative

How much would you trust information about health or medical topics from a doctor or other healthcare professional?



Health Information National Trends Survey, 2005 (HINTS, 2005) at www.cancercontrol.cancer.gov/hints; HINTS 2005 database, National Cancer Institute.

Risk

- Parents more likely to accept risks if:
  - Outweighed by potential benefits
  - Voluntary
  - Feel they have control
  - Safe to ask questions
  - Reframe the decision in terms of the child

Balancing Risks and Benefits

- Vaccines have to be considered in context
  - The disease risks are far, far greater than the risk of a serious effect from the vaccine
- Delaying or withholding vaccines will not lessen the risk of autism
  - It will increase the time during which children are at risk for infections

Balancing Risks and Benefits

- "Serious allergic reaction (less than 1 out of a million doses)"
- A one in a million risk means that of the 4.1 million children born in the U.S. every year, four of these children could be affected
- 1-4 chance in 1000 of dying of measles if infected
- 1 chance in 2 of dying of tetanus if infected

What to Do

- Ask parents & patients if they have any concerns about vaccines.
  - Just because they are getting a vaccine doesn't mean they don't have questions
- Know the common myths & the answers
- Prepare ourselves to communicate effectively

59

What to Do

- Think & talk in positive sound bites
  - TMI (too much information)
    - Complicated answers may confuse or lose parents
    - Get a read for what they need
  - Communications theory
    - Listeners remember no more than 3 points

60

Message Mapping

- Vaccines are good.
  - They are highly protective against serious illnesses, many of which can be fatal
- Vaccines are safe.
  - Most side effects are minor and soon go away
  - Serious reactions are extremely rare
- Vaccines have to be considered in context
  - The disease risks are far, far greater than the risk of a serious effect from the vaccine

61

Message Mapping

- Vaccine preventable diseases have not gone away, not even in the U.S.
  - These diseases are common in most of the rest of world, including in some cases Europe
  - International travel is continually reintroducing these diseases into the U.S.
  - Once here, they often spread easily

Responding to Questions

- Do vaccines cause autism?
  - Cause of autism is not known
  - What is known-Autism spectrum disorders are genetic
  - Possible role of environmental factors

Questions

Q) Does MMR cause autism?
A) No

Q) Does thimerosal cause autism?
A) No

Prepare: Printed studies in office , marked websites, materials from AIM Kit, AAP

Questions?
What about Aluminum in Vaccines?

- Aluminum
  - Used as an adjuvant since 1926
  - Only aluminum salts can be used as a adjuvant in the U.S.
  - Boosts the immune response to the vaccine
  - Reviewed in 2000 by National Vaccine Program Office-no changes to vaccine recommendations were needed

Vaccine Education Center, Children's Hospital of Philadelphia

Quantities of Aluminum in Vaccines

Pneumococcal Vaccine	.125 mg/dose
Diphtheria-tetanus-acellular pertussis (DTaP) vaccine	Less than 0.17 to less than 0.625 mg/dose
Hib, Hib/HepB, Peds Hep A vaccine	0.225 mg/dose to .25 mg/dose
Hepatitis B vaccine (Hep B)	0.25 to 0.5 mg/dose
DTaP/inactivated polio/ Hep B vaccine	Less than0.85 mg/dose

Quantities of Aluminum in Other Things

Breast milk	0.04 milligrams per liter (mg/L)
Ponds, lakes, streams	0.1 mg/L
Infant formula	0.225 mg/L
Soy-based formula	0.46 to 0.93 mg/L
Buffered aspirin	10 to 20 mg/tablet
Antacid	104-208 mg/tablet

Aluminum in perspective

- So in the infant's first six months
  - Infants receive 4.4 mgs of aluminum from vaccines
  - Breast-fed infants ingest 7 mgs of aluminum
  - Formula-fed infants ingest 38 mgs of aluminum
  - Soy formula-fed infants ingest 117 mgs of aluminum

Vaccine Education Center, Children's Hospital of Philadelphia

Questions about Alternative Schedules

Q) Do multiple vaccines cause harm?
Can I delay vaccines?

A) 1. Vaccines are tested with other vaccines
2. Number of antigens is less today
14 vaccines have 150 components
3. Immunologic challenge from vaccines is small compared to what they get everyday
4. Children have a big capacity to respond
5. No research that delaying shots is safer

What you can do!

- Read what's being written in the media for parents and about legislation, locally and nationally
- Search the web and read postings
- Have resources on hand to give to patients from state & local health depts, CDC, AAP, AAFP, IAC
- Stand by the science!
- If a legislative battle is brewing in your state or nationally, get involved
- Get on list-servs so you can share info with colleagues

Helpful websites

- www.ecbt.org *and* www.vaccinateyourbaby.org
- www.immunize.org *and* www.vaccineinformation.org
- www.cdc.gov/vaccines
- www.vaccine.chop.edu
- www.aap.org *and* www.cispimmunize.org
- www.nnii.org
- www.preventinfluenza.org
- www.michigan.gov/immunize
- www.aimtoolkit.org

Free Immunization Update for You and Your Staff

- An Update includes:
  - Current recommendations
  - Vaccine administration
  - Appropriate vaccine storage and handling
  - Proper documentation and follow-up
  - CME Level 1 and nursing credits available
- Provides individualized assistance in optimizing your immunization delivery system